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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,923	05/14/2007	Manpreet S. Wadhwa	PC027698A	4848

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PATENT DEPARTMENT
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EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

NOTIFICATION DATE	DELIVERY MODE
03/01/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,923	WADHWA ET AL.	
	Examiner	Art Unit	
	FOZIA M. HAMUD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/13/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1a. Receipt of Applicants' amendment and arguments, filed on 13 December 2010 is acknowledged.

Status of Claims:

1b. Claims 1-15 are pending and under consideration.

Information Disclosure Statement:

2. The information disclosure statement filed on 13 December 2010 has been received and complies with the provisions of 37 CFR §1.97 and §1.98. The references have been considered as to the merits.

Maintenance of Previous Rejection:

Claim Rejections - 35 USC § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al (U.S. Patent 6,448,225, issued on 10 September 2002) in view of Patel, Suman, (US patent 5,358,708, issued on 25 October 1994), further in view of Cleland et al, (Pharmaceutical research, 1996, Vol. 13, No. 10, pages 1464-1475).

The instant claim 1 is drawn to a formulation consisting of a therapeutically effective amount of a human growth hormone, (recombinant) in an aqueous solution, a buffer that maintains the pH of the formulation at a pH of 5 to 7, a *non-ionic surfactant*, a polymer stabilizer, methionine, and one or more optional excipients selected from the group consisting of a divalent cation present in a magnesium salt selected from the group consisting of magnesium hydroxide, magnesium chloride, magnesium sulfate, magnesium citrate, and magnesium edentate; a tonicity agent; and a preservative, wherein the formulation remains stable after at least one freezing and subsequent thawing event. Claims 2-12, recite specific concentrations and/or excipients. Claim 13 recites that the formulation remains in solution after exposure to three or more freeze-thaw events, claims 14-15 further limit the invention regarding time that the formulation remains stable and that total deamidation is measured by anion exchange HPLC.

U.S. Patent 6,448,225, (O'Connor et al) teach a stable aqueous formulation of human growth hormone, (recombinant) comprising human growth hormone, citrate, phosphate, Tris, succinate, or histidine buffer, (2 mM to 50 mM), providing pH 5.5 to pH 7, nonionic surfactant, (polysorbate 20 or 80, 0.1% to 5%), polyethylene polymer, tonicity agent, (sorbitol) and preservative, (phenol or benzyl alcohol), (see column 3, lines 1-3 and column 3, line 30 to column 4, line 22). O'Connor et al teach that their

formulation is stable upon storage for 6 to 18 months at 2 to 8^0 C and that deamidation was measured by anion exchange chromatography, (see column 5, line 51 to column 6, line 50).

However, '225 reference does not teach formulations of human growth hormone that also comprise methionine or polyethylene glycol.

US patent 5,358,708, (Patel, Suman) teaches aqueous formulations of an interferon, a granulocyte-macrophage colony-stimulating factor or an interleukin having extended storage lifetimes by adding methionine to said formulations, (see column 3, line 59 to column 4, line 33, figures 1 and 2 and claims).

Cleland et al teach stable formulations of human growth hormone that are formulated with polyethylene glycol for stability and improved yield, (see abstract, pages 1467-1468).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made, to modify the formulations of human growth hormone taught by '225 patent by adding methionine and polyethylene glycol to said formulation with great expectation of success by following the techniques taught by the '708 and Cleland et al references, which teach the benefit of using methionine to extend the storage lifetimes of formulations of recombinant proteins and the benefit of using polyethylene glycol for improved yield, respectively.

One of ordinary skill would have achieved the predictable result of obtaining a stable liquid formulation of human growth hormone with extended storage lifetime with a great expectation of success by following the techniques taught by the O'Connor et al,

Patel and Cleland et al references. One of ordinary skill would have been able to manipulate concentrations of buffers and excipients to obtain optimum stability. The person of ordinary skill in the art would have been motivated to make human growth hormone in a stable liquid formulation with extended storage lifetime, because growth hormone is used clinically to treat children's growth disorders and adult growth hormone deficiency. Therefore, it is of great importance to obtain stable human growth hormone formulations with extended storage lifetime to improve efficacy and prevent undesirable byproducts such as aggregates during processing and storage. Accordingly, the invention, taken as a whole, is prima facie obvious over the cited prior art.

Response to Applicants' Arguments:

Applicants submit that the instantly claimed formulation of hGH which also requires methionine and polyethylene glycol is non-obvious in view of the combination of '225, '708 and Cleland. Applicants reviewed and cited case laws, regarding the proper test of obviousness such as the teaching, suggestion, motivation (TSM) test. Applicants submit that the Examiner has admitted that the '225 patent does not teach aqueous formulations of human growth hormone that comprise methionine or polyethylene glycol and then states that modification of '225 with the combination of the teachings of the '708 patent and Cleland renders the instantly claimed invention obvious. Applicants argue that the lack of teaching of a formulation comprising hGH, methionine and polyethylene glycol is not cured by combining the '225 patent with the '708 patent and Cleland. Applicants contend that the '708 patent teaches formulations of an interferon, granulocyte-macrophage colony stimulating factor or an interleukin in a

buffer with methionine or histidine, and there is no mention of a formulation comprising hGH in the '708 reference and also no reference of a formulation comprising polyethylene glycol. Applicants submit that in addition, there is no suggestion in '708 that use of methionine would be successful in stabilizing an entirely different protein such as hGH and that the '708 recognized that there is considerable uncertainty in arriving at stabilized formulations of proteins. Applicants argue that the '708 patent clearly recognized that different formulations of the proteins interferon, granulocyte-macrophage colony stimulating factor or an interleukin behave differently depending on the nature of the protein itself. Applicants submit that the '708 inventors recognized that there is uncertainty in obtaining a stabilized formulation of a protein based on the nature and identity of the specific protein employed and that the '708 patent does not equate all proteins and does not mention nor suggest in any way that hGH could be stabilized by addition of methionine or histidine. Applicants contend that one of ordinary skill in the art, in view of '708, would not know whether or not methionine would work to stabilize an aqueous formulation of hGH as instantly claimed.

These arguments have been considered, but are not deemed persuasive. The Examiner takes no issue with Applicant's general comments regarding the legal standard for obviousness. Applicants are correct in that all the limitations of the claimed invention are not taught by any one of the cited references, but the combined teachings of the cited references render the claimed invention obvious. The ‘225 patent teaches all of the limitations of the claimed invention, except for the use of methionine and polyethylene glycol. The ‘708 patent is relied upon for the use of methionine as a

stabilizer for three ***diverse*** proteins, (G-CSF, interferon-alpha and IL-4) at ***different*** pH conditions, and showed that the addition of methionine extended storage life for all three proteins, (see examples 1-4). Although the '708 patent does not teach that hGH is stabilized using methionine, it teaches three different proteins and shows that they were all stabilized by the use methionine. With respect to Applicants' argument that different proteins may behave differently depending on the nature of the protein itself, the '708 provides guidance as to how to obtain the best concentrations, conditions and effective amounts of methionine for each protein, (see column 4, lines 19-29). The '708 patent does not teach that their formulations would not stabilize proteins other than G-CSF, interferon-alpha or interleukin-4.

Applicants also submit that one of ordinary skill in the art would not be motivated to modify the combination of O'Conner, Patel and Cleland to arrive at the instantly claimed invention since there is no motivation to do so. The obviousness rejection is based on combination of Patel et. al., which references the use of methionine as a stabilizer without the use of a polymer stabilizer for the following proteins: interleukin, interferon, and granulocyte macrophage colony stimulating factor with the O'Conner hGH formulation which lacks both the polymer stabilizer and methionine. Cleland provides an emulsified aqueous/organic formulation of hGH used for encapsulation into microspheres which requires the presence of an organic solvent (ethyl acetate or methylene chloride) and wherein the aqueous sodium phosphate buffer is at pH 8, which is at a higher pH than the instantly claimed formulation, and which may or may not contain polyethylene glycol to stabilize the hGH from being denatured by the organic

solvent. Applicants argue that one of ordinary skill in the art would not be motivated to modify the combination of O'Conner, Patel and Cleland since the use of methionine as a stabilizer is not only protein specific, but can also be pH specific and is therefore methionine is not known as a common stabilizer. Applicants submit that the literature also discloses that the use of methionine as a stabilizer is very dependent upon the protein and the conditions of the formulation. In fact, even the use of methionine in formulating granulocyte macrophage colony stimulating factor referenced in Patel et. al., has been shown to only be a stabilizer at acidic conditions and have no effect when formulating at alkaline conditions. Applicants argue that Cleland would have to be substantially modified since the hGH formulations described therein require the presence of an organic solvent and the pH of the buffer would need to be lowered.

These arguments have been considered, but are not deemed persuasive. The ‘225 patent teaches all of the limitations of the claimed invention, except for the use of methionine and polyethylene glycol. The ‘708 patent is relied upon for the use of methionine as a stabilizer and the Cleland et al reference is relied upon by its disclosure of human growth hormone that is formulated with polyethylene glycol, which improved both stability and yield. Thus, there is a strong motivation to modify the growth hormone formulations of the ‘225 reference by using methionine as a stabilizer, because the '708 reference teaches that the advantages of using methionine is that it extends storage life. One would also be motivated to modify the growth hormone formulations of the ‘225 reference by adding polyethylene glycol to said formulations, because Cleland et al reference teaches that polyethylene glycol increases stability and yield. With respect to

Applicants' argument that the Cleland formulations are in a pH 8 buffer, and that the literature discloses that the use of methionine has been shown to only be a stabilizer at acidic conditions and have no effect when formulating at alkaline conditions, is irrelevant, because the '708 patent teaches the optimum pH for methionine.

Applicants submit that Example 6 provided in the instant patent application shows the advantageous stability profile of the formulation of hGH with methionine and a polyethylene glycol polymer stabilizer as instantly claimed. Applicants respectfully submit that the improved stability profile provides a formulation of hGH that is not suggested by the cited references.

It is not disputed that Example 6 discloses stabilized hGH, however, the combined teachings of '225, '708 and Cleland et al render the claimed invention obvious.

Conclusion:

4. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery J. Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fozia Hamud
Patent Examiner
Art Unit 1647
22 February 2011

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